PATENT
Docket No.: 1290-7281

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Bouchard, et al.	Group Art Unit: 1203
Serial No.	:	08/162,984	Examiner: B. Trinh
Filed	:	December 8, 1993	
For	:	NEW TAXOIDS, THEIR PREPARATION AND PHARMACEUTICAL COMPOSITION CONTAINING THEM	

DECLARATION OF FRANCOIS LAVELLE

Honorable Commissioner of Patents & Trademarks
Washington, D.C. 20231

Sir:

I, FRANCOIS LAVELLE, make the following declaration:

1. I am employed as the Director of the Department of Biologie, Service de Cancérologie by RHÔNE-POULENC RORER RECHERCHE-DÉVELOPPEMENT, the wholly owned subsidiary of RHÔNE-POULENC RORER S.A., the assignee of the above-identified application (the "'984 Application").

2. I received a Doctorat ès Sciences at the Université de Paris. I have been employed in the position of Director of the Department of Biologie, Service de Cancérologie for 17 years. Included in my responsibilities is the supervision of biological assays of compounds for anti-tumor activity and in particular the assay of compounds in the taxoid family for properties of tumor cell growth inhibition and tumor cell death. I am a co-author on numerous publications including those listed in attached Appendix I.

Based upon my professional and educational background and experience, I am familiar with the subject relating to TAXOL®, TAXOTERE® anti-tumor compounds, their derivatives and their pharmacological profiles including their anti-tumor properties. In this declaration, I will present and explain the results of studies comparing the anti-tumor properties of the cyclopropyl taxoid compound referred to herein as Compound I with its closest structural analogues disclosed in the '984 application and U.S. Patent No. 5,254,580 (10/19/93) to Chen et al. assigned to Bristol-Myers Squibb (the "'580 patent").

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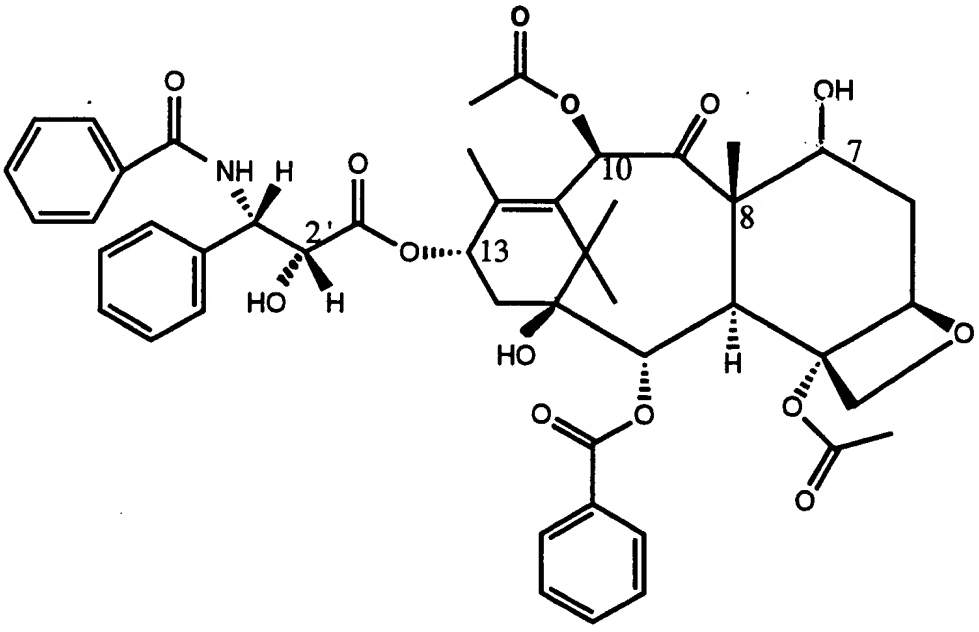
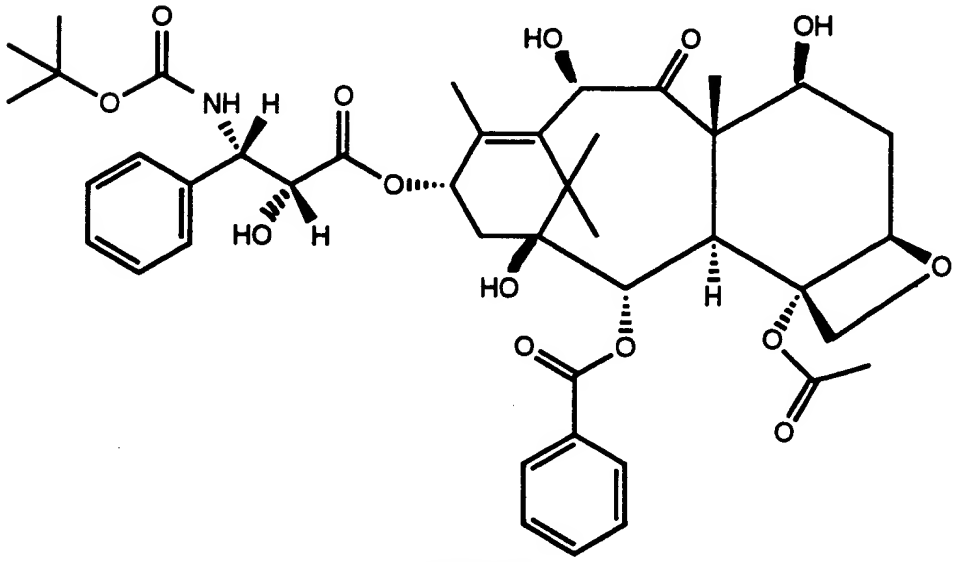
3. I organized and directly supervised the pharmacological study of taxoid compounds disclosed in the "'580 patent". Among the TAXOL and TAXOTERE derivatives disclosed therein is the compound I will refer to as Compound I, N-debenzoyl-N-t-butoxycarbonyl-7-deoxy-8-desmethyl-7,8-cyclopropataxol which is referenced in Example 23 and claim 7 of the '580 patent.

4. Compound I is described and supported in the '984 application at page 4, lines 21-24, and claimed by virtue of claim 53 and claim 102.

5. For purposes of more easily comprehending the comparative data which follows, the structural formulae of TAXOL and TAXOTERE anti-tumor compounds are provided hereinbelow:



TAXOL

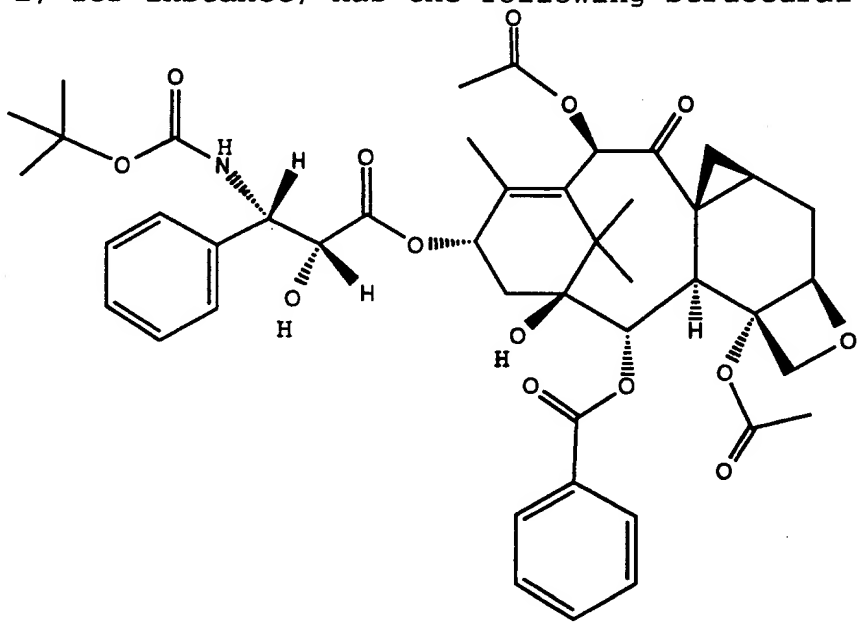


TAXOTERE

)81)

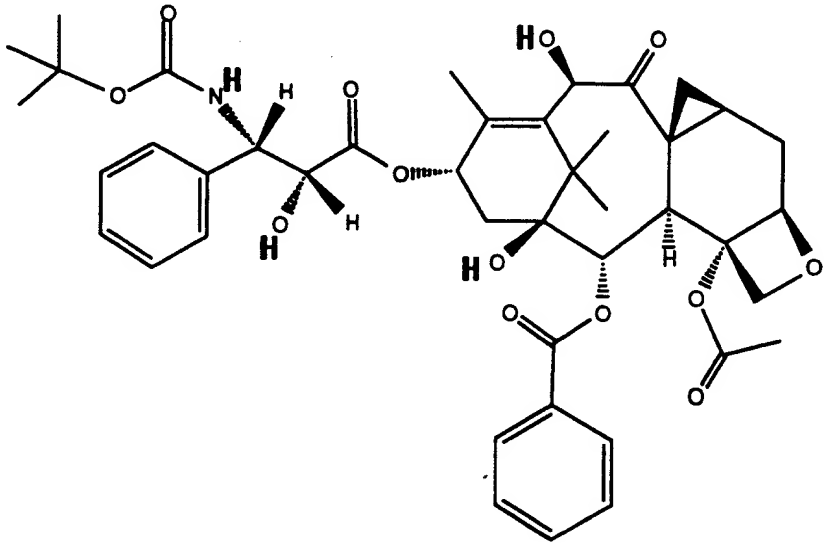
There are two structural differences between the two above compounds: at the 10-position TAXOL has an acetyl group (OAc) whereas TAXOTERE has an hydroxy group (OH), and on the nitrogen at the 3' position of the side chain, TAXOL has a phenylcarbonyl group (C_6H_5CO-) whereas TAXOTERE has a tert-butoxy-carbonyl group (t-BuOCO-).

The derivatives disclosed in the '580 patent and the '984 application are derivatives of TAXOL and TAXOTERE in which the 7,8-position is modified to provide a cyclopropyl derivative. Compound I, for instance, has the following structural formula:

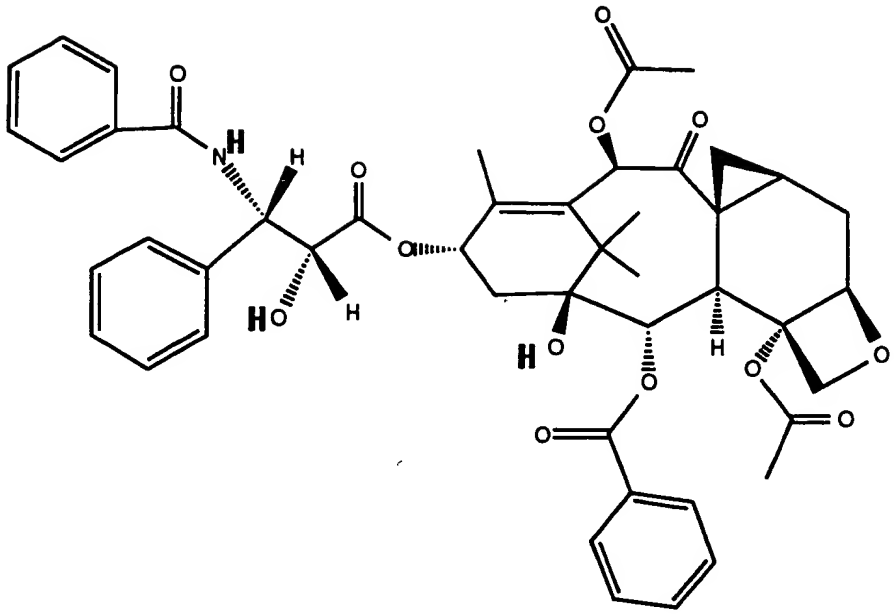


COMPOUND I

6. In my position at RHÔNE-POULENC RORER, I have supervised biological studies which compare the anti-tumor properties of Compound I with its two most closest structurally related compounds (compounds II and III), both of which are disclosed in the '580 patent and whose formulae are provided hereinbelow:



II



III

Compound II, having the TAXOTERE nucleus, differs from Compound I in that it has an hydroxy group instead of the acetoxy group at position 10.

Compound III, having the TAXOL nucleus, differs from Compound I in that instead of the t-butoxy group on the side-chain, has a phenyl group.

7. The biological studies which I supervised compared the in vitro and in vivo anti-tumor properties of Compounds I, II and III. In the in vitro study, the anti-tumor properties of compounds I, II and III were compared against two different tumor cell lines characterized by either the presence or the absence of the multi-drug resistance gene.

Description of the In Vitro Test

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The *in vitro* activity is evaluated in the P388 murine leukemia cell line and the P388 murine leukemia cell line resistant to doxorubicine and ~~containing~~ the multi-drug resistance gene (P388/DOX). FL 12.27-94

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FL. 12/27/94

3x10⁵ cells/ml were ~~ground~~ grown for 96 hours in the presence of various drug concentrations. Cells were then incubated for 16 hours with 0.02% natural red, washed and lyzed with 1% SDS (sodium dodecyl sulphate).

The incorporation of the dye reflecting the cellular growth was assayed by optical density measurement at 540 and 346 nm.

The concentration of the drugs resulting in 50% growth inhibition (IC_{50}) was then determined: the lower the IC_{50} value the higher the ~~selectivity~~ potency of the compound.

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The lower the ratio (IC_{50}-P388/DOX) / (IC_{50}-P388), the "Resistance Factor R", the higher the activity of the compound as an effective tumor cell growth inhibitor of multi-drug resistant cell lines.

The results of the comparative in vitro study are presented in the following table A.

TABLE A

Compound	IC_{50} (µg/ml) P 388	P 388/DOX	Resistance Factor R
I	0.03	0.25	8
II	0.03	0.45	15
III	0.085	1.80	21

Description of the In Vivo Test

In the in vivo study, antitumor activity of compounds I, II and III were evaluated in B16 melanoma bearing mice wherein tumors were implanted as subcutaneous bilateral fragments in B6 D2F1 mice.

Description of the methodology

The animals necessary to begin a given experiment were pooled and implanted - subcutaneously bilaterally with 30 to 60 mg tumor fragment on day 0 with a 12 gauge trocar. Bilateral implants were used to insure a more uniform burden per mouse and thus reduce the requirement for a greater number of mice per group.

For an early stage tumor treatment, the tumor-bearing animals were again pooled before unselected distribution to the various treatment and control groups.

For an advanced stage treatment, the solid tumors were allowed to grow to the desired size range (animals with tumors not in the desired range were excluded). The mice were then pooled and unselectively distributed to the various treatment and control groups.

Non tumor bearing animals (NTBA) were often matched to tumor-bearing groups and given the same route, dose and schedules. In this way, drug-induced toxicity can be clearly separated from the effects of the tumors.

Chemotherapy was started within 3 to 24 days after tumor implantation. Mice were checked daily and adverse clinical reactions were noted.

Each group of mice was weighed as a whole three to five times weekly until the weight nadir was reached. The groups were weighed once or twice weekly until the end of the experiment.

Tumors were measured with a caliper twice or three times weekly until the tumors reached 2,000 mg or until the animal died (whichever comes first).

Solid tumor weights were estimated from two dimensional tumor measurements

$$\text{Tumor weight (mg)} = \frac{\text{length (mm) x width 2 (mm2)}}{2}$$

The day of death was recorded. Surviving animals were killed and macroscopic examination of the thoracic and abdominal cavities was carried out. In some cases, tissue samples were submitted to histological evaluation.

- End point for assessing antitumor activity

Antitumor activity evaluation was done at the highest non-toxic dosage (HNTD). A dosage producing 20 % weight loss nadir (mean group) or 20 % or more drug deaths, was considered an excessively toxic dosage. Animal body weights included tumor weights.

- Tumor growth inhibition (T/C)

The treatment and control groups were measured when the median of the control group tumors reached approximately 750 to 1,200 mg the median tumor weight of each group was determined.

The T/C value in percent is an indication of antitumor effectiveness:

$$\text{T/C (\%)} = 100 \times \frac{\text{median tumor weight of the treated groups}}{\text{median tumor weight of the control groups}}$$

According to NCI (National Cancer Institute) standards, a T/C < 42 % (score : +) is the minimal level to declare activity. A T/C < 10 % (score : ++) is considered to indicate high antitumor activity and is the level used by NCI to justify further development.

- Tumor growth delay

T and C are the median times (in days) required for the treatment group and the control group tumors respectively to reach predetermined size (usually 750 to 1,000 mg). Tumor free survivors are excluded from these calculations and tabulated separately.

This value is the more significant one as it allows the quantification of the tumor cell kill.

- Determination of the tumor doubling time (Td)

Td is estimated from the best fit straight line from a log linear growth plot of the control group tumors in exponential growth (100 to 1,000 mg range).

- Quantification of tumor cell kill

For subcutaneous growing tumors, the total log cell kill is calculated from the following formula:

$$\text{log cell kill (gross or total)} = \frac{\text{T - C value in days}}{3.32 \times \text{Td}}$$

where T-C is the tumor growth as described above and Td is the tumor volume doubling time in days.

The log cell kill value can be converted to an arbitrary activity rating with the following table:

Activity	Duration of treatment (5-20 days) $\log_{10}$ kill gross
Highly active++++	> 2.8
+++	2.0 to 2.8
++	1.3 to 1.9
+	0.7 to 1.2
Inactive-	<0.7

The results of the comparative in vivo study are presented in the following Table B.

TABLE B

Compound	T/C x 100	Score	Log cell kill	Score
I	6	++	2.7	++
II	17	+	1.0	+
III	53	-		-

In the experiments : tumor (B16 melanoma) grafted s.c. on day 0 in mice; i.v. treatment on days 5,7 and 9.

Score (T/C x 100):T/C<10:++;T/C between 10 and 42:+;T/C>42:-

Score (Log cell kill):<0.7:-; between 1 and 2:+;>2:++

CONCLUSION

8. Based upon the results of the biological evaluation shown in the above Tables A and B, it is my professional opinion that Compound I is the superior anti-tumor compound in comparison to the closely related compounds II and III in that compound I is about 2-3 fold more effective than compounds II and III in vitro and by the T/C x 100 and the log cell kill in the in vivo study.

It is my further opinion that the superiority of Compound I over compounds II and III is unexpected in view of their close structural similarities, one having the TAXOTERE nucleus, the other the TAXOL nucleus, and their apparently minor structural differences as described above.

9. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1011 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the '984 Application or any patent issuing thereon.

Date: December 27, 1994 By: Francois Lavelle

Francois Lavelle

APPENDIX I

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